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ART UNIT	PAPER NUMBER
1654	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	09/772,445	KLEINMAN ET AL.	
	Examiner	Art Unit	
	RONALD T. NIEBAUER	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40,53-61,133-136 and 173-182* is/are pending in the application.

4a) Of the above claim(s) *9,10,12,20,21,37 and 178-182* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11,13-19,22-36,38-40,53-61,133-136 and 173-177* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/11/08, 2/21/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants amendments and arguments filed 2/11/08 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed is herein withdrawn.

Claims 41-52,62-132,137-172 are cancelled. Claims 9-10,12,20-21,37 remain withdrawn as being drawn to non-elected subject matter.

Applicant has amended claims 14,16,17,18,19,39,54,56-60,134.

Claims 173-182 have been added as new claims.

Newly submitted claims 178-182 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

As noted in the restriction requirement dated 10/5/04 the instant invention (Group I) is drawn to methods of promoting wound healing.

Claim 182 (compare original group III) is drawn to a composition.

The composition of claim 182 and the instant invention are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the composition can be used in a materially different process such as for immunoassays or molecular weight markers or for the cleavage of DNA (see DNAseI) or for the reversing of anticoagulation activity (see fragmin).

Claim 181 is drawn to a method of diagnosing.

The method of claim 181 and the instant method are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different designs, modes of operation, and effects (MPEP § 802.01 and § 806.06). In the instant case, the different inventions have different active steps (obtain sample, detect level, compare level for claim 181; administration of a polypeptide for the instant invention) and are designed for different effects (diagnosing vs. treating).

Claim 180 is drawn to a method of promoting growth of a prosthetic tissue or organ

The method of claim 180 and the instant method are directed to related processes. The related inventions are distinct if: (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed are designed for different patient populations (those with wounds vs. those with a prosthetic tissue or organ). Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

Claims 178-179 is drawn to a method of preventing comprising administering an agent.

The method of claims 178-179 and the instant method are directed to related processes. The related inventions are distinct if: (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed designed for different patient populations (those with wounds vs. those with a disease) and the

active component administered is different since the instant claims are drawn to a polypeptide of a particular sequence or a conservative variant while claims 178-179 are drawn to an agent that decreases or increases the activity of a polypeptide. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the inventions require a different field of search restriction for examination purpose as indicated is proper.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 178-182 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 1-8,11,13-19,22-36,38-40,53-61,133-136,173-177 are under consideration.

This office action is arranged such that the maintained rejections are cited in the first section and then the section NEW GROUNDS FOR REJECTION cites the new rejections.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1,5-8,11,23,25-28,33-36,38-40,133-136 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus …") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a

method of obtaining the claimed sequence." MPEP § 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163. While all of the factors have been considered, a sufficient amount for a *prima facie* case are discussed below.

In the instant case, the claims are drawn to methods comprising administering a polypeptide or a conservative variant having wound-healing activity.

(1) Level of skill and knowledge in the art:

The level of skill in the art is high with regard to methods of wound healing. The level of knowledge in the art is low regarding understanding the functional effects of varying a particular peptide sequence given that the effects of substitutions cannot be predicted a priori.

(2) Partial structure:

A conservative variant is defined (page 11), however specific examples of the many variations are not provided. There are hundreds of possible polypeptides that fall within the scope of the claims. Since there are a substantial variety of polypeptides possible within the genus, the limited examples do not constitute a representative number of species and do not sufficiently describe the genus claimed (see *Gostelli* above).

(3) Physical and/or chemical properties and (4) Functional characteristics:

The peptides and variants are recited as having wound-healing activity. There is no disclosed correlation between this functional characteristic and any structure. One of skill in the art would not recognize which variants are sufficient to have wound-healing activity and one could not a priori predict the properties.

(5) Method of making the claimed invention:

Methods of making peptides are well known in the art, however given the unpredictable nature of amino acid substitution methods of making peptides and peptide variants such that the peptides maintain wound-healing properties is not well established.

As stated *supra*, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that claim(s) 1,23 is/are broad and generic, with respect to all conservative variants encompassed by the claims. The possible structural variations are numerous to any variant. Although the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond those compounds specifically disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus. While having written description peptides identified in the specification tables and/or examples, the specification does not provide sufficient descriptive support for the myriad of compounds embraced by the claims.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Response to Arguments written description

Applicants argue that the description of the invention is quite detailed. Applicants argue that polypeptides are identified in the specification from page 9 line 21 through page 10 line 28.

Applicants state that the term "conservative variant" is defined in the specification . Applicants argue that conservative variants of LKKTET include active variations such as FKHVVP. Applicant has submitted references regarding actin-binding or actin-sequestering polypeptides.

Applicant's arguments filed 2/11/08 have been fully considered but they are not persuasive.

Based on the arguments and reconsideration it is noted that claims 2-4,24,29-32 are adequately described and the previous written description rejection has been withdrawn on these claims. In particular it is noted that such claims read on specific polypeptides (thymosin B4 or isoforms thereof) and that the claims do not read on conservative variants.

It is noted that as defined and claimed, conservative variants are not limited to a specific number of variations. In fact, there can be any number of variations. It is noted that conservative variants as defined on page 11 lines 1-6 includes examples of specific replacements and the like. In determining the scope of and the like it is pointed out that on page 12 (first full paragraph) of the reply dated 2/11/08 applicant stated that conservative variants of LKKTET includes active variations in other actin-binding proteins such as FKHVVP. In comparing LKKTET and FKHVVP it is noted that and the like must be interpreted very broadly since F (an aromatic) is substituted for L (a nonpolar aliphatic); V (a nonpolar aliphatic) is substituted for E (acidic); P (nonpolar) is substituted for T (polar). As such, the definition of "conservative variants" is very broad and includes nearly any polypeptide. Further, it is noted that although applicant argues about actin-binding or actin-sequestering polypeptides such polypeptides are not specifically recited in the claims.

Although applicant argues that the specification and the prior art both provide examples, such specific examples are not recited in the claims and the examples are not representative of the genus of "conservative variants" as defined in the instant specification. In particular it is noted that the claims do not limit the conservative variants to specific polypeptides recited in the specification or prior art. Based on the definition in the specification the term conservative variant has to be broadly interpreted (see MPEP section 2111).

For these reasons, the reasons above, and the reasons set forth previously the rejection is maintained.

Claims 1-8,11,23-36,38-40,133-136 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for promoting wound-healing with specific peptides in vivo for the cornea and skin, does not reasonably provide enablement for methods of making and using any peptide variants for any type of wound healing. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the

amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

In the instant case, the claims are drawn to methods comprising administering a polypeptide or a conservative variant having wound-healing activity. The wounds are associated with eye, skin, uro-genital, gastro-intestinal, cardiovascular, muscle, connective, neural tissues, or healing of any and all wounds associated with diseases or conditions selected from arthritis, osteoporosis, musculo-skeletal disorders, bums, skin diseases, neurodegenerative disorders, nerve diseases, bone diseases, heart disease, retinal damage, all skin damage, cardiovascular diseases, an ischemia, atherosclerosis, fibrotic disorder, sclerotic disorder, cancer and all cell proliferative disorders

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

The claims are drawn to conservative variants which include amino acid substitutions. However, the knowledge in the art is low with regard to understanding which amino acid sequences will have a particular function given that the effects of substitutions cannot be predicted a priori. With regards to the effect of amino acid substitution in a peptide or protein, the art is unpredictable.

MATHISON (US Patent 6,586,403 B1) teaches that "Restriction on the amino acid substitutions that are tolerated in analogues of FEG/feG are described […] although a theory for the rational substitution of amino acids in to the peptides that permits the prediction of biological activity of specific peptides is not apparent. For example, it is not obvious which aromatic or

aliphatic substitutions in position 1 of tri- or dipeptides would possess biological activity in the four assays examined" (column 12, lines 22-30).

Further, MPEP § 2144.08 states, "The effect of a conservative substitution on protein function depends on the nature of the substitution and its location in the chain. Although at some locations a conservative substitution may be benign, in some proteins only one amino acid is allowed at a given position. For example, the gain or loss of even one methyl group can destabilize the structure if close packing is required in the interior domains. James Darnell *et al.*, *Molecular Cell Biology* 51 (2d ed. 1990)."

(5) The relative skill of those in the art:

The level of skill in the art is high regarding wound healing in general, however, the knowledge in the art is low with regard to understanding which amino acid sequences will have a particular function given that substitutions cannot be predicted a priori.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

Examples (such as example 1) are provided in which a specific peptide is tested for wound healing functionality. However, the specification does not provide examples for the breadth of the peptide variants possible. Further, examples of making specific variants with wound-healing properties have not been provided. Specifically, one of skill in the art would not accept that all variants described would function in wound healing.

(8) The quantity of experimentation necessary:

Experimentation is required in numerous areas particularly related to how to make specific variants with wound healing properties and determination if it would be a useful

composition against the plethora of associated conditions. Considering the state of the art as discussed by the references above, particularly with regards to the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

Response to Arguments enablement

Applicants argue that the claims are drawn to conservative variants of LKKTET. Applicants state that numerous references demonstrate the efficacy of the claimed polypeptides.

Applicant's arguments filed 2/11/08 have been fully considered but they are not persuasive.

Based on the arguments and reconsideration it is noted that claims 2-4,24,29-32 are adequately enabled. In particular it is noted that such claims read on specific polypeptides (thymosin B4 or isoforms thereof) and that the claims do not read on conservative variants.

As discussed above, as defined and claimed, conservative variants are not limited to a specific number of variations. In fact, there can be any number of variations. It is noted that conservative variants as defined on page 11 lines 1-6 include examples of specific replacements and the like. In determining the scope of and the like it is pointed out that on page 12 (first full paragraph) of the reply dated 2/11/08 applicant stated that conservative variants of LKKTET includes active variations in other actin-binding proteins such as FKHVVP. In comparing LKKTET and FKHVVP it is noted that and the like must be interpreted very broadly since F (an aromatic) is substituted for L (a nonpolar aliphatic); V (a nonpolar aliphatic) is substituted for E

(acidic); P (nonpolar) is substituted for T (polar). As such, the definition of "conservative variants" is very broad (see MPEP section 2111) and includes nearly any polypeptide.

Further, it is noted that a conclusion of lack of enablement is based on evidence at the time the application was filed (see MPEP section 2164.01(a)). In the instant case, it is noted that many of the references cited by applicant are clearly after the filing date. Further, the examples in the references are not for polypeptides of the same scope as the "conservative variants" described in the instant specification. It is noted that all the claims currently rejected for lack of enablement are drawn to "conservative variants".

For these reasons, the reasons above, and the reasons set forth previously the rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the

reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-3,5-7,11,13-14,16-18,22-29,33-36,38-39,53-55,57-59,61,133-135 remain rejected under 35 U.S.C. 102(e) as being anticipated by Mann (US 6,030,948). It is noted that the 102(e) date for Mann is Dec. 19, 1997 based on MPEP section 706.02(f)(1) section III for a patent that is not from an international application and in which there is no international application in the continuity chain.

Briefly the claims are drawn to methods comprising administering/contacting with a particular composition.

Mann teach a composition (claim 1, Tables 13-16) containing thymosin fraction 5. The thymosin fraction 5 includes both thymosin β4 (which comprises the sequence LKKTET) and thymosin α1 (which itself can augment the wound healing process – see page 11 of specification of the current invention). Claim 8 of Mann also teaches combinations of thymosin α1 and thymosin β4 thus meeting the compostion limitations recited in claims 1-3,5-7,11,13-14,16-18,22-29,33-36,38-39,53-55,57-59,61,133-135 of the instant invention. Mann teach a method of applying this composition to the scalp (claim 8). Prior to application to the scalp, an acid peel (i.e. chemical peel) solution is applied to the scalp and then removed. The removal of the acid peel solution results in the removal of an outer layer of the skin and results in abrasion/damage/lesions/wounds on the skin. Mann teach that the composition can be applied topically as a lotion or gel (column 3 lines 52-63) and can be used for males or females (Tables 13-16). Since the composition is applied to the skin it is applied to a tissue and specifically to

epithelial cells thus meeting the patient population of claims 1-3,5-7,11,13-14,16-18,22-29,33-36,38-39,53-55,57-59,61,133-135 of the instant invention.

Section 2111.02 of the MPEP states:

> During examination, statements in the preamble reciting the purpose or intended use of the claimed invention must be evaluated to determine whether the recited purpose or intended use results in a structural difference (or, in the case of process claims, manipulative difference) between the claimed invention and the prior art. If so, the recitation serves to limit the claim. See, e.g., In re Otto, 312 F.2d 937, 938, 136 USPQ 458, 459 (CCPA 1963)

In the instant case, limitations such as promoting migration (claim 53) do not result in a manipulative difference and do not serve to limit the claims.

Response to Arguments 102e rejection

Applicants argue that they have submitted a declaration under 37 CFR 1.131 antedating the Mann patent. Applicants state that the experiments in the exhibit were conceived, supervised and/or conducted by the inventors in the United States and establish conception and reduction to practice prior to December 19,1997. Applicants argue that the Mann patent has been removed as a prior art reference.

Applicant's arguments filed 2/11/08 have been fully considered but they are not persuasive.

The declaration filed on 2/11/08 under 37 CFR 1.131 has been considered but is ineffective to overcome the Mann reference.

The Mann reference is a U.S. patent or U.S. patent application publication of a pending or patented application that claims the rejected invention. An affidavit or declaration is inappropriate under 37 CFR 1.131(a) when the reference is claiming the same patentable

invention, see MPEP § 2306. If the reference and this application are not commonly owned, the reference can only be overcome by establishing priority of invention through interference proceedings. See MPEP Chapter 2300 for information on initiating interference proceedings. If the reference and this application are commonly owned, the reference may be disqualified as prior art by an affidavit or declaration under 37 CFR 1.130. See MPEP § 718.

Section 706.02(b) of the MPEP states:

> When the claims of the reference U.S. patent or U.S. patent application publication and the application are directed to the same invention or are obvious variants, an affidavit or declaration under 37 CFR 1.131 is not an acceptable method of overcoming the rejection.

In the instant case, the Mann patent (a US patent) claims (for example claim 8) anticipate claims of the instant invention as discussed above. Thus, the applicants submission of the 1.131 declaration is insufficient to overcome the rejection.

Section 715.05 of the MPEP states:

> When the reference in question is a noncommonly owned U.S. patent or patent application publication claiming the same invention as applicant and its publication date is less than 1 year prior to the presentation of claims to that invention in the application being examined, applicant's remedy, if any, must be by way of 37 CFR 41.202 instead of 37 CFR 1.131.

Thus, the applicants submission of the 1.131 declaration is insufficient to overcome the rejection.

Further, it is noted that the declaration is drawn to the administration of a single active agent, either thymosin α1 or thymosin β4. However, claim 3 for example is drawn to the administration of the active agent along with a further agent. As such, the declaration is not fully commensurate with the rejected claims. As noted above claim 8 of Mann teach administration of compositions including both thymosin α1 and thymosin β4.

Section 715.02 of the MPEP states:

> Even if applicant's 37 CFR 1.131 affidavit is not fully commensurate with the rejected claim, the applicant can still overcome the rejection by showing that the differences between the claimed invention and the showing under 37 CFR 1.131 would have been obvious to one of ordinary skill in the art, in view of applicant's 37 CFR 1.131 evidence, prior to the effective date of the reference(s) or the activity.

In the instant case, the applicant has not shown that the differences between the claimed invention and the showing would have been obvious to one of ordinary skill in the art.

For these reasons, the reasons above, and the reasons set forth previously the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 4,8,15,19,30-32,40,56,60,136 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Mann (US 6,030,948) as discussed above, and Siebert et al. (US 5,591,716), and Luedders et al. (US 4,261,982), and Rahim et al. (US 4,863,906).

Briefly the claims are drawn to methods comprising administering/contacting with a particular composition.

As stated above, Mann teach methods of administering a composition comprising thymosin β4.

Mann does not expressly teach thymosin as a recombinant or synthetic peptide (claim 8,19 of the current invention), contacting *in vitro* or *ex vivo* (claim 60), the use of a specific component such as sterile water (claim 136), the use of transforming growth factor beta (claim 4,15,30 for example), the use of zinc (claims 31-32 for example), or the use on the eye (claim 40,56 for example).

It is well-known in the art that a recombinant peptide (as recited in claims 8,19 of the instant invention) can be substituted for a purified peptide while maintaining an expectation of predictable results since the primary sequence of the protein is retained. Similarly, the substitution of sterile water (as recited in claim 136 of the instant invention) for water (as used in the preparation of the thymosin) is well-known. Hence, it would have been obvious to one of skill in the art to substitute one component for the other to achieve a predictable result since the active component (thymosin) is still present.

Regarding contacting *in vitro* or *ex vivo* (as recited in claim 60 of the instant invention), since *in vivo* work is suggested by Mann, it would be obvious to one of skill in the art to try and

determine if similar results could be obtained *in vitro* so that experimental results could be achieved in a more cost effective manner in a laboratory setting instead of requiring human subjects.

As stated above, Mann teach methods of administering a composition comprising thymosin β4. Siebert teach a composition comprising TGFβ (column 18 lines 1-3) (as recited in claims 4,15,30 of the instant invention) for wound healing (claim 8). Since all of the prior art elements were known in the art one of skill in the art would have combined the elements for the same purpose (wound healing) and the combination would have yielded predictable results.

As stated above, Mann teach methods of administering a composition comprising thymosin β4. Luedders teach a composition (for example claim 5) including zinc ions (as recited in claims 31-32 of the instant invention) for topical application to the skin. Leudders teach that zinc has been linked to wound healing (column 1 last paragraph). Since all of the prior art elements were known in the art one of skill in the art would have combined the elements for example, to enhance the wound healing process, and the combination would have yielded predictable results since the active component (thymosin) is still present.

As stated above, Mann teach methods of administering a composition comprising thymosin (column 6 line 20). Rahim teach a therapeutic composition including compositions which can be administered to the eye (column 5 lines 21-22) (as recited in claims 40, 56 of the instant invention). Since all of the prior art elements were known in the art one of skill in the art would have combined the elements and the combination would have yielded predictable results since the active component (thymosin) is still present.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments 103 rejection

Applicants argue that 'As to the obviousness rejection, the Siebert et al., Luedders et al., and Rahim et al references cannot be combined to render the present claims unpatentable, since no combination of these references discloses or renders obvious the present claims'.

Applicant's arguments filed 2/11/08 have been fully considered but they are not persuasive.

It is noted that the applicants argument is not particularly specific and does not point to reasons why the references cannot be combined. As described above the declaration filed on 2/11/08 under 37 CFR 1.131 has been considered but is ineffective to overcome the Mann reference. The rejection above points to the specific claim limitations that are met by the references.

Regarding applicants assertion that references cannot be combined it is pointed out that it has been recently held that "Neither §103's enactment nor *Graham*'s analysis disturbed the Court's earlier instructions concerning the need for caution in granting a patent based on the combination of elements found in the prior art." KSR v. Teleflex, 550 U.S. ___, 82 USPQ2d 1385, 1389 (2007). The KSR court stated that "a combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." KSR at 1389.

Furthermore, The KSR court concluded that "obvious to try" may be an appropriate test under 103. The Supreme Court stated in *KSR*

> When there is motivation
> "to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, ___, 82 USPQ2d 1385, 1397 (2007).

In the instant case, the claimed elements (thymosin fraction 5, transforming growth factor, and zinc) were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. Further, it is noted that the substitution of one known element (sterile water, recombinant peptide) for another (water, native peptide) would have yielded predictable results to one or ordinary skill in the art at the time of the invention. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole

was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

For these reasons, the reasons above, and the reasons set forth previously the rejection is maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The examiner has identified three copending Applications/Patents which have been rejected under Double Patenting. Because of Applicant's prolific Patent and Application portfolio, the burden is shifted to Applicant to identify all relevant Applications and Patents and to include said Applications and Patents on any terminal disclaimer filed.

Claims 1-3,5-8,11,13-14,16-19,22-25,27-29,33-36,38-39,53-55,57-59,61,133-135 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 and 10-12 of copending Application No. 10/714,405. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '405 application teaches methods of treating/healing of blisters, sores or skin degeneration (which are wounds and tissue as in the instant invention) by application of proteins comprising the LKKTET sequence or Thymosin beta four (the proteins of the instant invention). The methods encompass systemic and topical application of the compositions, to include the instantly claimed formulations (gel, crème, paste, lotion, spray, suspension, dispersion, salve, hydrogel, or ointment). Additionally, the '405 application claims teach administering an agent that stimulates the proteins comprising the LKKTET sequence or Thymosin beta four as in the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-7,13-18,23-28,30,33-36,39,53-55,57-59,61,133-135 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7-16 of copending Application No. 11/284,408. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '408 application teaches methods of administering compositions to the skin comprising thymosin beta four (for example, claim 7), transforming growth factor (claim 8), for topical treatment (for example, claim 7).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-8,11,13-19,22-36,38-40,53-61,133-136 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over allowable claims 3-8,29-35 (which have been indicated as allowable 3/29/07) of application 10/853,505. Although the conflicting claims are not identical, they are not patentably distinct from each other because '505 teach a composition comprising thymosin beta four (claim 5) and the since the specification is the same as that of the current invention one having ordinary skill in the art would have been motivated to use the particular combinations and methods recited in the specification and have expectation for success.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned 10/714,405; 11/284,408; 10/853,505; discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Response to Arguments double patenting

Applicants argue that they will file appropriate terminal disclaimers or cancel conflicting claims from other applications upon an indication that claims of the present application are otherwise allowable.

Applicant's arguments filed 2/11/08 have been fully considered but they are not persuasive.

No terminal disclaimer has been filed and no conflicting claims have been cancelled so the rejection has not been overcome.

For these reasons, the reasons above, and the reasons set forth previously the rejection is maintained.

NEW GROUNDS FOR REJECTION

Below are the new grounds of rejection necessitated by applicants amendments/new claims.

NEW *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 173,175,177 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus …") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a

method of obtaining the claimed sequence." MPEP § 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163. While all of the factors have been considered, a sufficient amount for a *prima facie* case are discussed below.

In the instant case, the claims are drawn to methods comprising administering a polypeptide or a conservative variant having wound-healing activity.

(1) Level of skill and knowledge in the art:

The level of skill in the art is high with regard to methods of wound healing. The level of knowledge in the art is low regarding understanding the functional effects of varying a particular peptide sequence given that the effects of substitutions cannot be predicted a priori.

(2) Partial structure:

A conservative variant is defined (page 11), however specific examples of the many variations are not provided. There are hundreds of possible polypeptides that fall within the scope of the claims. Since there are a substantial variety of polypeptides possible within the genus, the limited examples do not constitute a representative number of species and do not sufficiently describe the genus claimed (see *Gostelli* above).

(3) Physical and/or chemical properties and (4) Functional characteristics:

The peptides and variants are recited as having wound-healing activity. There is no disclosed correlation between this functional characteristic and any structure. One of skill in the art would not recognize which variants are sufficient to have wound-healing activity and one could not a priori predict the properties.

(5) Method of making the claimed invention:

Methods of making peptides are well known in the art, however given the unpredictable nature of amino acid substitution methods of making peptides and peptide variants such that the peptides maintain wound-healing properties is not well established.

As stated *supra*, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that claim(s) 1,23 is/are broad and generic, with respect to all conservative variants encompassed by the claims. The possible structural variations are numerous to any variant. Although the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond those compounds specifically disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus. While having written description peptides identified in the specification tables and/or examples, the specification does not provide sufficient descriptive support for the myriad of compounds embraced by the claims.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Response to Arguments written description

Since applicants arguments are relevant to the new rejection the arguments will be addressed. Applicants argue that the description of the invention is quite detailed. Applicants

argue that polypeptides are identified in the specification from page 9 line 21 through page 10 line 28. Applicants state that the term "conservative variant" is defined in the specification . Applicants argue that conservative variants of LKKTET include active variations such as FKHVVP. Applicant has submitted references regarding actin-binding or actin-sequestering polypeptides.

Applicant's arguments filed 2/11/08 have been fully considered but they are not persuasive.

Based on the arguments and reconsideration it is noted that claims 2-4,24,29-32 are adequately described and the previous written description rejection has been withdrawn on these claims. In particular it is noted that such claims read on specific polypeptides (thymosin B4 or isoforms thereof) and that the claims do not read on conservative variants.

It is noted that as defined and claimed, conservative variants are not limited to a specific number of variations. In fact, there can be any number of variations. It is noted that conservative variants as defined on page 11 lines 1-6 includes examples of specific replacements and the like. In determining the scope of and the like it is pointed out that on page 12 (first full paragraph) of the reply dated 2/11/08 applicant stated that conservative variants of LKKTET includes active variations in other actin-binding proteins such as FKHVVP. In comparing LKKTET and FKHVVP it is noted that and the like must be interpreted very broadly since F (an aromatic) is substituted for L (a nonpolar aliphatic); V (a nonpolar aliphatic) is substituted for E (acidic); P (nonpolar) is substituted for T (polar). As such, the definition of "conservative variants" is very broad and includes nearly any polypeptide. Further, it is noted that although applicant argues

about actin-binding or actin-sequestering polypeptides such polypeptides are not specifically recited in the claims.

Although applicant argues that the specification and the prior art both provide examples, such specific examples are not recited in the claims and the examples are not representative of the genus of "conservative variants" as defined in the instant specification. In particular it is noted that the claims do not limit the conservative variants to specific polypeptides recited in the specification or prior art. Based on the definition in the specification the term conservative variant has to be broadly interpreted (see MPEP section 2111).

Claims 173,175,177 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for promoting wound-healing with specific peptides in vivo for the cornea and skin, does not reasonably provide enablement for methods of making and using any peptide variants for any type of wound healing. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

> The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the

amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

In the instant case, the claims are drawn to methods comprising administering a polypeptide or a conservative variant having wound-healing activity. Claim 177 is drawn to a method of prevention. Please note that the term "prevent" is an absolute definition which means to stop from occurring and, thus, requires a higher standard for enablement than does "therapeutic" or "treat", especially since it is notoriously well accepted in the medical art that the vast majority of afflictions/disorders suffered by mankind cannot be totally prevented with current therapies (other than certain vaccination regimes). The wounds are associated with eye, skin, uro-genital, gastro-intestinal, cardiovascular, muscle, connective, neural tissues, or healing of any and all wounds associated with diseases or conditions selected from arthritis, osteoporosis, musculo-skeletal disorders, bums, skin diseases, neurodegenerative disorders, nerve diseases, bone diseases, heart disease, retinal damage, all skin damage, cardiovascular diseases, an ischemia, atherosclerosis, fibrotic disorder, sclerotic disorder, cancer and all cell proliferative disorders

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

The claims are drawn to conservative variants which include amino acid substitutions. However, the knowledge in the art is low with regard to understanding which amino acid sequences will have a particular function given that the effects of substitutions cannot be

predicted a priori. With regards to the effect of amino acid substitution in a peptide or protein, the art is unpredictable.

MATHISON (US Patent 6,586,403 B1) teaches that "Restriction on the amino acid substitutions that are tolerated in analogues of FEG/feG are described […] although a theory for the rational substitution of amino acids in to the peptides that permits the prediction of biological activity of specific peptides is not apparent. For example, it is not obvious which aromatic or aliphatic substitutions in position 1 of tri- or dipeptides would possess biological activity in the four assays examined" (column 12, lines 22-30).

Further, MPEP § 2144.08 states, "The effect of a conservative substitution on protein function depends on the nature of the substitution and its location in the chain. Although at some locations a conservative substitution may be benign, in some proteins only one amino acid is allowed at a given position. For example, the gain or loss of even one methyl group can destabilize the structure if close packing is required in the interior domains. James Darnell *et al.*, *Molecular Cell Biology* 51 (2d ed. 1990)."

(5) The relative skill of those in the art:

The level of skill in the art is high regarding wound healing in general, however, the knowledge in the art is low with regard to understanding which amino acid sequences will have a particular function given that substitutions cannot be predicted a priori.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

Examples (such as example 1) are provided in which a specific peptide is tested for wound healing functionality. However, the specification does not provide examples for the

breadth of the peptide variants possible. Further, examples of making specific variants with wound-healing properties have not been provided. Specifically, one of skill in the art would not accept that all variants described would function in wound healing.

(8) The quantity of experimentation necessary:

Experimentation is required in numerous areas particularly related to how to make specific variants with wound healing properties and determination if it would be a useful composition against the plethora of associated conditions. Considering the state of the art as discussed by the references above, particularly with regards to the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

Response to Arguments enablement

Since applicants arguments are relevant to the new rejection the arguments will be addressed. Applicants argue that the claims are drawn to conservative variants of LKKTET. Applicants state that numerous references demonstrate the efficacy of the claimed polypeptides.

Applicant's arguments filed 2/11/08 have been fully considered but they are not persuasive.

Based on the arguments and reconsideration it is noted that claims 2-4,24,29-32 are adequately enabled. In particular it is noted that such claims read on specific polypeptides (thymosin B4 or isoforms thereof) and that the claims do not read on conservative variants.

As discussed above, as defined and claimed, conservative variants are not limited to a specific number of variations. In fact, there can be any number of variations. It is noted that conservative variants as defined on page 11 lines 1-6 include examples of specific replacements and the like. In determining the scope of and the like it is pointed out that on page 12 (first full paragraph) of the reply dated 2/11/08 applicant stated that conservative variants of LKKTET includes active variations in other actin-binding proteins such as FKHVVP. In comparing LKKTET and FKHVVP it is noted that and the like must be interpreted very broadly since F (an aromatic) is substituted for L (a nonpolar aliphatic); V (a nonpolar aliphatic) is substituted for E (acidic); P (nonpolar) is substituted for T (polar). As such, the definition of "conservative variants" is very broad (see MPEP section 2111) and includes nearly any polypeptide.

Further, it is noted that a conclusion of lack of enablement is based on evidence at the time the application was filed (see MPEP section 2164.01(a)). In the instant case, it is noted that many of the references cited by applicant are clearly after the filing date. Further, the examples in the references are not for polypeptides of the same scope as the "conservative variants" described in the instant specification. It is noted that all the claims currently rejected for lack of enablement are drawn to "conservative variants".

NEW *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 177 is rejected under 35 U.S.C. 102(b) as being anticipated by Golstein et al. (US 5,578,570 as cited in the IDS 2/21/08).

Golstein teach the administration of thymosin B4 (claim 1 for example) to a mammal.

It is noted that claims 177 is drawn to methods of prevention. Since a method of prevention is used on a patient population prior to the onset of the ailment/disorder, any patient population is available for preventative administration. The patient population described by Goldstein includes mammals (claim 1) and therefore meets the patient population of claims 177 of the instant invention. Further, Goldstein teach the active step (administration of of thymosin B4 (claim 1)) of claims 177 of the instant invention.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claim 177 is rejected under 35 U.S.C. 102(e) as being anticipated by Mann (US 6,030,948). It is noted that the 102(e) date for Mann is Dec. 19, 1997 based on MPEP section 706.02(f)(1) section III for a patent that is not from an international application and in which there is no international application in the continuity chain.

Mann teach a composition (claim 1, Tables 13-16) containing thymosin fraction 5. The thymosin fraction 5 includes both thymosin β4 (which comprises the sequence LKKTET) and thymosin α1 (which itself can augment the wound healing process – see page 11 of specification of the current invention). Claim 8 of Mann also teaches combinations of thymosin α1 and thymosin β4 thus meeting the compostion limitations recited in claim 177 of the instant invention. Mann teach a method of applying this composition to the scalp (claim 8). Prior to application to the scalp, an acid peel (i.e. chemical peel) solution is applied to the scalp and then removed. The removal of the acid peel solution results in the removal of an outer layer of the skin and results in abrasion/damage/lesions/wounds on the skin. Mann teach that the composition can be applied topically as a lotion or gel (column 3 lines 52-63) and can be used for males or females (Tables 13-16). Since the composition is applied to the skin (i.e. a skin wound) it is applied to a tissue and specifically to epithelial cells thus meeting the patient population of claim 177 of the instant invention.

Further, it is noted that claims 177 is drawn to methods of prevention. Since a method of prevention is used on a patient population prior to the onset of the ailment/disorder, any patient population is available for preventative administration.

NEW *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 173-176 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mann (US 6,030,948) as applied to claims 1,13,23,53 above and further in view of Mann (US 6,030,948).

As discussed above Mann teach claims 1,3,23,53

In claim 8 Mann teaches that the thymic extract is administered. Although Mann teach amounts of the thymic extract Mann does not expressly teach the amounts of the specific components such as thymosin B4.

Please note, since the Office does not have the facilities for examining and comparing Applicants' composition with the composition of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. *See In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980), and "as a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith." *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972).

It is noted that Mann teach amounts of thymic extract ranging from 0.1 to 10 percent by weight. Table 14 shows that thymosin fraction 5 can be included at between 0.01-10 weight percent.

It would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions (e.g. polypeptide concentrations), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation. ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). *See* MPEP § 2145.05).

NEW *Double Patenting*

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection

is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The examiner has identified three copending Applications/Patents which have been rejected under Double Patenting. Because of Applicant's prolific Patent and Application portfolio, the burden is shifted to Applicant to identify all relevant Applications and Patents and to include said Applications and Patents on any terminal disclaimer filed.

Claims 173-178 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 and 10-12 of copending Application No. 10/714,405. Although the conflicting claims are not identical, they are not patentably distinct from each other because the ‘405 application teaches methods of treating/healing of blisters, sores or skin degeneration (which are wounds and tissue as in the instant invention) by application of proteins comprising the LKKTET sequence or Thymosin beta four (the proteins of the instant invention).

Further, it is noted that claims 177 is drawn to methods of prevention. Since a method of prevention is used on a patient population prior to the onset of the ailment/disorder, any patient population is available for preventative administration.

It would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions (e.g. polypeptide concentrations), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation. ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). *See* MPEP § 2145.05).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 173-178 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7-16,29-47 of copending Application No. 11/284,408. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '408 application teaches methods of administering compositions to the skin comprising thymosin beta four (for example, claim 7), transforming growth factor (claim 8), for topical treatment (for example, claim 7). '408 teach the administration to skin specifically damaged skin (claim 29) and specifically to epithethial tissue (claim 38). '408 teach doses (claim 38,29) that meet the limitations of the instant claims.

Further, it is noted that claims 177 is drawn to methods of prevention. Since a method of prevention is used on a patient population prior to the onset of the ailment/disorder, any patient population is available for preventative administration.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 173-178 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13-23,26 of copending Application No. 11/917,869. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '869 application teaches methods of administering compositions to the skin comprising thymosin beta four (for example, claim 13), and specific doses (claim 23) as in the instant claims.

Further, it is noted that claims 177 is drawn to methods of prevention. Since a method of prevention is used on a patient population prior to the onset of the ailment/disorder, any patient population is available for preventative administration.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned 10/714,405; 11/284,408; 11/917,869; discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not

commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to RONALD T. NIEBAUER whose telephone number is (571)270-3059. The examiner can normally be reached on Monday-Thursday, 7:30am-5:00pm, alt. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ronald T Niebauer/
Examiner, Art Unit 1654

/Anish Gupta/
Primary Examiner, Art Unit 1654